Citation:

Makela P, Vahlberg T, Kantola I, Vesalainen R, Jula A. The effects of a six-month sodium restriction on cardiac autonomic function in patients with mild to moderate essential hypertension. *Am J Hypertension.* 2008; 21: 1,183-1,187.

PubMed ID: 18787516

Study Design:

Randomized controlled trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess the relationship between the blood pressure response and heart rate variability of subjects on non-pharmacological sodium restriction.

Inclusion Criteria:

- Subjects had mild to moderate uncomplicated essential hypertension. At time of recruitment had three one-week interval blood pressure readings, and the mean value of the last two measurements were within a range of 90-110 mmHg diastolic blood pressure (DBP) and/or 160-200mmHg systolic blood pressure (SBP)
- Previous anti-hypertensive medications had been withdrawn at least one year before the beginning of this study
- Subjects were not regularly taking oral contraceptives or any other drugs.

Exclusion Criteria:

- Patients with cardiomyopathy or hemodynamically significant cardiac valvular disease
- Other target organ complications of essential hypertension were excluded by means of clinical examination, routine biochemical tests and exercise electrocardiogram.

Description of Study Protocol:

Recruitment

Clients with uncomplicated essential hypertension from the occupational health service of 10 industrial plants and state offices in Turku, south-western Finland.

Design

Randomized controlled trial (RCT).

Blinding Used

None reported.

Intervention

- Intervention group: Reduction of daily sodium intake to≤ 70mmol, general advice to lose weight if necessary, general advice to reduce intake of saturated fats
- Control group: Not described.

Statistical Analysis

- Continuous variables were compared between intervention and control groups using two-sample T-test
- Changes within intervention and control groups were calculated using paired T-test
- Longitudinal data of characteristics and heart rate variability were analyzed using analysis of variance for repeated measurements. Models included main effects of time and group and the interaction between time and group.

Data Collection Summary:

Timing of Measurements

- Blood pressure (BP) measured at one month intervals throughout the study
- Sodium intake was checked three times during the study at zero, three and six months
- ECG carried out at beginning of study and at six months.

Dependent Variables

- Heart rate variability: Five time-domain HRV variables were analyzed: Mean RR interval, SD of normal RR intervals (SDNN), mean of the SDs of all RR intervals for five-minute segments of the entire recording (SDNNi), percentage of differences between adjacent normal RR intervals exceeding 50ms (pNN50), square root of the mean of squared differences between adjacent normal RR intervals (RMMSD). Six frequency-domain variables were calculated: Total (0.01-0.04 Hz), high frequency (HF, 0.15-0.40 Hz), LF (0.04-0.15 Hz), very LF (0.01-0.04 Hz), ultra -LF power (0.00001-0.01 Hx) and the LF/Hf ratio.
- BP measurements: Subjects were requested to avoid caffeine-rich beverages during the morning of BP measuring and were requested to avoid smoking for a least 30 minutes before the BP measurements were taken.

Independent Variables

- Assignment to low- or normal-sodium diet for six months
- Sodium intake: Calculated from seven-day food records using the Nutrica computer program for food and nutrient calculation developed at the Social Insurance Institution, Finland
- Sodium intake was checked by urinary excretion and measured by flame photometry.

Control Variables

None.

Description of Actual Data Sample:

- *Initial N:* 91 patients (31 women, 60 men)
- *Attrition (final N):* 80 were randomized, 40 to each group
- *Age:* 38-50 years
- *Ethnicity:* Finnish
- *Other relevant demographics:* None reported
- *Anthropometrics:* SBP was slightly higher in the intervention group compared to the control group at baseline (P=0.04), but otherwise the groups were comparable
- *Location:* Turku, Finland.

Summary of Results:

Key Findings

- SBP and DBP decreased significantly more in intervention group (SBP from 149.9±14.7mmHg to 130.3±11.8mmHg and DBP from 98.0±6.4mmHg to 87.1±6.2mmHg, time x group, P<0.001) after six months of salt restriction
- No significant (NS) differences in the change between groups could be detected
- 24-hour urinary sodium decreased significantly (P<0.001) in intervention group, but increased in the control group (time x group, P<0.001)
- NS changes or differences in changes were seen in any time or frequency-domain variables of heart rate variability
- No correlation in changes of HRV were found in relation to sodium intake during the study.

Table: Significant Differences Between Subject Characteristics (Baseline and Six Months)

Characteristics	Intervention		Control	
	Baseline	Six months	Baseline	Six months
N	40	40	40	40
Weight (kg)a	81.7±15.7	78.9±14.5**	80.0±16.2	80.4±15.8
BMI (kg/m^2)b	27.3±4.5	26.4±4.2**	27.3±4.3	27.4±4.1
Energy consumption (kJ per day)a	9,240.7±2,282.2	7,838.0±1,786.9**	8,966.93±2,505.0	8,234.8±2,161.2*

[a]For time effect, P < 0.001; ANOVA for repeated measurements.

[b]For time x group interaction, P<0.001; ANOVA for repeated measurements. *P<0.05, **P<0.001 compared to baseline within the group paired T-test.

Table: Characteristics of Blood Pressure, Heart Rate and Urine Sodium in the Beginning of the Study and at Three and Six Months (N=80)

	SBP (mmHg)a	DBP (mmHg)a	Heart Rate	dU-sodium (mmol)a
Control zero months	143.9±11.5	96.7±4.6	73.0±7.6	181.1±77.3
Intervention zero months	149.9±14.7*	98.0±6.4	76.2±9.9	196.8±92.2
Control three months	139.5±12.5	94.9±6.1	71.5±9.5	178.4±65.9
Intervention three months	132.1±12.2*	88.4±6.8**	73.6±10.0	71.1±51.4
Control six months	136.4±10.1	92.6±5.7	69.5±9.3	191.6±67.5
Intervention six months	130.3±11.8*	87.1±6.2**	71.2±8.2	89.8±65.8**

[a]For time x group interaction, P<0.001: ANOVA for repeated measurements. For time effect P<0.001: ANOVA for repeated measurements. *P<0.05 intervention vs. control. **P<0.001 interventions vs. control.

Other Findings

- Energy intake decreased in intervention group (P<0.001) and in control group (P<0.05)
- BMI diminished significantly in the intervention group (P<0.001), but remained unchanged in the control group and the difference in change between groups was significant (time x group, P<0.001)
- Level of physical activity did not change in either group (data shown in other publication).

Author Conclusion:

- A prolonged six-month non-pharmacological treatment with sodium restriction decreased both SBP and DBP significantly. However, no changes were seen in the cardiac parasympathetic nervous control as measured by heart rate variability
- Non-cardiac autonomic mechanisms are likely to predominate in the BP-lowering effect of salt restriction.

Reviewer Comments:

- *Significant differences between groups at baseline. Descriptive details missing in this study report, such as, how anthropometric data was collected (self report vs. measured) and how often sodium intake was collected and analyzed*
- *The study intervention program was claimed to be described in detail in another publication. That published reference was from 1990. The author does acknowledge a potential confounder in results may be change in energy intake in the intervention group.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	No
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	No
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes

3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	No
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A

6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	No
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	No
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes

	8.7.	If negative findings, was a power calculation reported to address type 2 error?	Yes
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes